REMARKS

Claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 are pending in the application. Claims 88, 96, 98, and 99 are withdrawn. Claims 3-9, 11, 16-20, 22-24, 26, 29, 30, 32-39, 43, 44, 49-55, 58-76, 82-83, 85-87, 89-95, 97, and 100 have been cancelled without prejudice or disclaimer. Claims 1, 21, 47, and 48 are amended. Accordingly upon entry of the amendment, claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-81, 84, and 101 are pending in the application.

The claims have been amended to claim more fully the recited subject matter and to make minor editorial changes. Support for the amendments can be found throughout the claims and specification as filed, and is discussed in more detail below. Specifically, support for the amendment of claim 1 can at least be found in the specification at page 15, lines 1-6, page 16, line 29, and claim 21 as filed. Support for the amendment of claim 47 can at least be found in the specification at page 8, lines 1-7, and claim 48 as filed. Support for the amendment of claim 48 can at least be found in the specification as filed at Table 1. No new matter has been added.

Amendment and cancellation of the claims herein are not to be construed as acquiescence to any rejections/objections set forth in the pending Office Action and/or any previous Office Actions and were done solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed or similar claims in this or one or more subsequent patent applications.

Sequence Compliance

The Office Action at pages 2-3 has stated that the application is not in compliance with 37 C.F.R. §§1.821-1.825. Applicants submit concurrently herewith a sequence listing in compliance with 37 C.F.R. §§1.821-1.825, and a sequence listing statement. Applicants have amended the specification to direct the entry of the sequence listing into the specification at the appropriate place, and to insert a sequence identifier (SEQ ID NO: 1) to reference the sequence set forth in Figure 2. No new matter is being added by the amendments, as the sequence set forth in Figure 2 was originally present in the specification as filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the sequence compliance objection.

Specification/Drawings

The Office Action at page 3 has objected to the specification for incorporating subject matter by reference to GenBank accession numbers. Specifically, the Examiner has alleged that GenBank accession numbers are ineffective because "GenBank accession numbers are not identifying static sequences, but rather can be amended/changed over time and do not necessarily reflect the sequence contemplated by Applicant." Applicants respectfully disagree.

The GenBank record is updated to reflect any changes in the sequences under a GenBank accesion number. This policy is stated at www.ncbi.nlm.nih.gov/Sitemap/samplerecord.html#VersionB:

> If there is any change to the sequence data (even a single base), the version number will be increased, e.g., U12345.1 → U12345.2, but the accession portion will remain stable.

Moreover, the history of each GenBank entry is carefully maintained. As stated at www.ncbi.nlm.nih.gov/Sitemap/samplerecord.html#ModificationDateB:

> If you need to know the first date of public availability for a specific sequence record, send a message to info@ncbi.nlm.nih.gov. We will check the history of the record for you, and let you know the date of first public release.

Thus, the GenBank accession number referencing a sequence is stable. Additionally, it is possible to know that a GenBank entry has been modified since the date of filing, and one is able inquire as to the exact date any modification to the sequence attached to an accession number has occurred. Therefore, Applicants respectfully submit that the sequences referenced in the specification correspond to those accessible at the date of filing, which are publicly accessible for retrieval.

The Office Action at page 3 has objected to the drawings and specification because they contain sequences which are not accompanied by sequence identifiers (SEQ ID NO). As set forth above, Applicants submit concurrently herewith a sequence listing, a sequence listing statement, and an amendment to the specification to reference the sequence set forth in Figure 2 as SEQ ID NO: 1.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the objections to the specification.

Claim Objections

The Office Action at page 3 has objected to claims 25 and 41, alleging that claims 25 and 41 are of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully disagree and traverse this basis for objection.

Regarding claim 25, the Examiner has alleged that claim 25 recites properties inherent in Iαl and Pαl, and therefore is not limiting of claim 25. As stated in the originally filed specification at page 7, lines 7-9, the molecular weights of Iαl and Pαl may vary, for example, if they are complexed with H4 or with H4 and each other:

> Iαl and Pαl have also been found to be complexed with H4, another heavy chain of Iαlp proteins. Certain embodiments of Iαlp compositions according to the invention contain H4 in complex with Pαl, Iαl, or both Pαl and Iαl.

The molecular weight range between about 60,000 to about 280,000 kDa describes a molecular weight range for Iαl and Pαl complexes. Thus, claim 25 limits claim 1.

Regarding claim 41, claim 41 is not broader in scope than claim 40, and, thus, claim 41 limits claim 40. As stated in the originally filed specification at page 7, lines 15-21, physiological proportions vary:

> Physiological proportions, as used herein is intended to include proportions found in a person or animal that is not suffering from an infection or condition, and/or the ratio of Iαl to Pαl that appears naturally in human plasma. Physiological proportions are usually from between about 60% to about 80% Iαl and between about 40% to about 20% Pαl. Physiological proportions may vary from these ranges due to normal variations in genetic makeup of subjects.

The range between about 60% to about 80% Iαl and between about 40% to about 20% Pαl falls within what the specification has described are physiological proportions. Thus, claim 41 limits claim 40.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the claim objections.

Claim Rejections – 35 U.S.C. §112

The Office has rejected claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 under 35 U.S.C. §112 as being allegedly indefinite. Applicants respectfully traverse the rejection.

The Examiner has alleged that "it is unclear how one can have a purity of IαIp ranging from about 85% to about 100% pure when the components with the IαIp are not fully defined. Applicants respectfully disagree.

The specification at page 16, lines 21-24, teaches that various methods for quantifying the degree of purification will be known to those of skill in the art, including determining the specific protein activity of a fraction, or assessing the number of polypeptides within a fraction by gel electrophoresis. As acknowledged by the Examiner, components of IαIp are described in the specification (see, e.g., page 7, lines 15 and 16; page 8, lines 16-19). Thus, it would be apparent that the purity of IαIp may be determined in terms of the proportion of these components to the total amount of protein in the composition. Alternatively, it is possible to define purity in terms of the specific activity of the composition. A high trypsin inhibitory specific activity is indicative of the purity of IαIp (see, e.g., Table 1).

The Examiner has alleged that claims 10, 12, 13, and 15 are indefinite because they do not limit the method of purifying the IαIp protein. Applicants respectfully disagree. The specification clearly states that a plasma fraction is "a fraction from an isolation or purification step, for example, chromatography, that was originally derived from blood plasma." (page 8, line 28 - page 9, line 6). That is, reciting the plasma fractions in the dependent claims further specifies the source of the starting material for the purification method being claimed. Thus, claims 10, 12, 13, and 15 are not indefinite.

The Examiner has alleged that claim 1 is indefinite when considered with claim 25 reciting the molecular weights of IαI and PαI. As set forth above, the specification states that the molecular weights of IαI and PαI may vary, for example, if they are

complexed with H4 or with H4 and each other (page 7, lines 7-9 of the originally filed specification). Between about 60,000 to about 280,000 kDa specifies a molecular weight range provided in the specification for the Iαl and Pαl complexes. Thus, claim 25 does not render claim 1 indefinite.

The Examiner has alleged that claim 41 is indefinite for reciting physiological ranges for Pαl and Iαl. As set forth above, the specification states that physiological proportions include the proportions found in a person or animal that is not suffering from an infection or condition, and/or the ratio of Iαl to Pαl that appears naturally in human plasma, and that physiological proportions may vary from these ranges due to normal variations in genetic makeup of subjects. (specification at page 7, lines 15-21). Between about 60% to about 80% Iαl and between about 40% to about 20% Pαl falls within what the specification has described are physiological proportions. Therefore, claim 41 is not indefinite as alleged.

The Examiner has alleged that claims 82 and 83 appear to be limitations of a method of isolation. Without in any way acquiescing to the reasoning underlying the rejection and in order to expedite prosecution, Applicants have canceled claims 82 and 83, thereby rendering the rejection moot as to these claims.

The Examiner has alleged that claim 86 lacks clear antecedent basis when considered with claim 85. Without in any way acquiescing to the reasoning underlying the rejection and in order to expedite prosecution, Applicants have canceled claims 85 and 86, thereby rendering the rejection moot as to these claims.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112.

Claim Rejections – 35 U.S.C. §102

The Office has rejected claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-80, and 101 under 35 U.S.C. §102 as being allegedly unpatentable over U.S. Patent No. 5,777,081 to Michalski et al. ("Michalski"). Applicants respectfully traverse the rejection.

In order to anticipate the invention as claimed, the cited referenced must teach each and every element of the claim. The presently claimed invention provides a blood

plasma-derived IαIp composition, containing a mixture of inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI) in a physiological proportion (e.g., a blood plasma-derived IαIp composition about 85% to about 100% pure; having a high trypsin inhibitory specific activity between about 1000 to about 2000 IU/mg; having a half-life greater than 1 hour), and a process for producing the IαIp composition comprising hydroxylapatite chromatography.

The Office Action at page 6 states that Michalski teaches the "isolation of a purified ITI fraction." However, Applicants' claimed IαIp composition, comprising a mixture of inter-alpha inhibitor protein (IαI) **and** pre-alpha protein (PαI), is distinct from the ITI fraction of Michalski. The ITI fraction of Michalski "consists of 3 polypeptide chains, two heavy H1 and H2 and one light" (col. 1, lines 18-20) and is a "glycoprotein with a molecular mass of 220,000 Da" (col. 1, lines 22-23). Michalski's ITI fraction does not contain **both** inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI). The ITI fraction described by Michalski contains only the inter-alpha inhibitor protein (IαI) of Applicants' claims ("bikunin [light chain] ... linked to 2 heavy polypeptide chains, H1 and H2" (page 1, lines 25-27); having a molecular weight of 225 kDa (page 1, lines 23-25). In particular, by SDS-PAGE analysis Michalski observed only "a **single major band** at a Mr of about 220,000 Da" (emphasis added; col. 3, lines 6-8). Michalski does not describe any other bands in the purified ITI fraction corresponding to any other proteins (e.g., PαI at 120 kDa).

The Office Action at page 6 alleges that "the same steps are practiced in Michalski, as instantly claimed and described in the instant examples." Applicants respectfully disagree. Without in any way acquiescing to the reasoning underlying the rejection and in order to expedite prosecution, the process claims have been amended to recite "wherein the purifying comprises hydroxylapatite chromatography." Michalski does not teach or suggest a hydroxylapatite step, as presently recited in the claims. Because Michalski does not teach or suggest such a purification step, Michalski does not anticipate the methods of the invention. Thus, Applicants' purification methods are distinct and distinguishable over those described in Michalski.

The Office Action at page 6 further alleges that "[the purified ITI of Michalski] must contain the same components in the same ratios, purity and possess the same

activities." Applicants respectfully disagree. Implicit in the Examiner's assertion is that the ITI purified according to Michalski inherently has the same properties of Applicants' IαIp composition because the same purification steps are used in both processes. However, as set forth above, the ITI purified according to Michalski does not comprise both inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI). Nor does the ITI purified by Michalski reliably have the same properties as the IαIp composition being claimed.

M.P.E.P. §2112 (IV) directs that the Examiner must provide rationale or evidence tending to show inherency:

> "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)...*In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). 'To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill'...*In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)...In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic **necessarily** flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). [Emphasis added.]

The current law of the Doctrine of Inherency indicates that the claimed property or effect must be the **necessary** consequence of the prior art disclosure. In other words, every time one conducts the prior art process, the claimed property or effect **must** occur. If one conducts the prior art method and does not get the claimed property or effect, then the claimed process is not inherent in the prior art.

As set forth above, Applicants' purification protocol includes hydroxylapatite chromatography. For example, procedures for producing the blood plasma-derived IαIp composition of the invention from fresh frozen plasma includes the steps of Cryoprecipitation, Solid-phase extraction, Ion exchange chromatography, (optionally, a Second ion-exchange chromatography or Affinity chromatography), and Hydroxylapatite chromatography (Figures 8a and 8b of the specification). The procedures described in Michalski do not recite a hydroxylapatite chromatography step, and, therefore, do not

provide an IαIp composition having the physiological ratio, purity, specific activity, and/or half-life, as recited in the claims.

That is, the steps recited in Michalski would not **inherently or necessarily** have resulted in obtaining the IαIp composition having the claimed properties of Applicants' IαIp composition. Although the steps used in Michalski include some of the same steps used by Applicants to obtain the blood plasma-derived IαIp composition of the invention, Applicants' purification protocols differ from those of Michalski. The purification methods described in Michalski are insufficient for **reliably** obtaining an IαIp composition comprising a mixture of inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI) and having the physiological ratio, purity, specific activity, and/or half-life, as recited in the claims. In contrast, the purification scheme disclosed in Applicants' specification (see, e.g., Figures 8a and 8b), is able to obtain an IαIp composition comprising a mixture of inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI) 85-100% pure using several chromatographic steps, including hydroxlapatite chromatography.

The Office Action at page 6 alleges that "Michalski additionally describes the resulting product as higher than 90% pure..." Nevertheless, Applicants respectfully disagree that the protocol of Michalski consistently provides an IαIp composition that comprises inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI) and has a purity in the range as recited in the claims. As set forth above, the purified ITI of Michalski did not contain PαI, as recited in Applicants' claims. That is, Michalski did not observe proteins other than ITI (i.e., IαI) by SDS-PAGE analysis (col. 3, lines 6-11) or high pressure gel filtration (col. 3, lines 12-13). Nor does the protocol of Michalski include a hydroxylapatite step. In particular, the hydroxylapatite step results in the removal of Factor II, X, and IV clotting factors (see, e.g., specification at Examples 3, 4, and 7). As evidence of the high purity of IαIp obtained by the methods of the invention, Applicants invite the Examiner's attention to Table 1 of the specification. Table 1 shows that the IαIp composition of the invention can achieve a purity of 98.27%. Thus, Michalski does not anticipate a purified IαIp composition comprising inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI) having 85-100% purity, even inherently.

Applicants' methods also enable one to purify an IαIp composition comprising inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI) and having a trypsin inhibitory specific activity between about 1000 to about 2000 IU/mg. The fact that the specific trypsin inhibitory activity is retained also reflects the physiological proportions and stability of Applicants' purified IαIp composition. Michalski does not describe a purified IαIp comprising inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI) having a specific trypsin inhibitory activity with the claimed range. In contrast, the purified ITI composition of Michalski has a specific trypsin inhibitory activity 420-500 mU/mg (col. 3, lines 19-22). As can be seen, practicing the protocol of Michalski does not **inherently result** in an ITI composition having all the properties as the IαIp of the claimed invention. Thus, the ITI composition of Michalski neither anticipates nor inherently anticipates the IαIp of the claimed invention.

Michalski teaches a protocol that is different from Applicants' protocol and would not have resulted in the IαIp composition with the properties recited in the claims, even inherently. Michalski does not teach a purification protocol that allows one to obtain an IαIp composition as claimed and that includes a hydroxylapatite step, which provides for the removal of residual contaminating coagulation factors (see, e.g., Example 3; page 33, lines 12-16), for achieving the purity (85% -100%), the specific activity (between about 1000 to about 2000 IU/mg), and stability (half-life greater than 1 hour) of the IαIp compositions being claimed. Specifically, Michalski does not describe an IαIp composition comprising a mixture of inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI), about 85% to about 100% pure or having a specific trypsin inhibitory activity between about 1000 to about 2000 IU/mg. Nor is there any evidence that using the methods of Michalski would necessarily have resulted in an IαIp composition having any of the properties of the IαIp compositions of the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 under 35 U.S.C. §102.

Claim Rejections – 35 U.S.C. §103

The Office has rejected claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 under 35 U.S.C. §103 as being allegedly unpatentable over Michalski in view of PCT Publication No. WO 01/63280 to Lim et al. ("Lim"). Applicants respectfully disagree and traverse the rejection.

In order to make out a *prima facie* showing of obviousness, the Examiner must establish that there is some motivation in one or the other of the cited references or in the state of the art at the time the invention was made to combine the references, the combination of references must teach or suggest each and every element of the claimed invention, and there must be some reasonable expectation of success in making and using the invention.

As acknowledged by the Examiner on page 8 of the Office Action, Michalski does not "specifically indicate what the therapeutic use is." The Examiner has further cited Lim as an alleged remedy for this deficiency of Michalski.

However, the claims as currently amended recite a blood plasma-derived IαIp composition, containing a mixture of inter-alpha inhibitor protein (IαI) and pre-alpha protein (PαI) in a physiological proportion "about 85% to about 100% pure"; "having a high trypsin inhibitory specific activity between about 1000 to about 2000 IU/mg;or "having a half-life greater than 1 hour", and a process for producing the IαIp composition "comprising hydroxylapatite chromatography." As set forth above, Michalski does not teach or suggest such a blood plasma-derived IαIp composition and/or a process for producing such an IαIp composition. Likewise, Lim also does not teach or suggest the IαIp composition as presently claimed or a process for producing an IαIp composition comprising hydroxylapatite chromatography. Therefore, Lim does not make up for the deficiencies in Michalski.

Thus, there is nothing in either of the cited references or in the state of the art at the time the invention was made that provides one of ordinary skill in the art with motivation to combine the references in the manner proffered by the Examiner. Assuming for the sake of argument that there were such motivation, the combination does not teach or suggest each and every element of the claimed invention because neither reference teaches or suggests a blood plasma-derived IαIp composition (about

85% to about 100% pure; having a high trypsin inhibitory specific activity between about 1000 to about 2000 IU/mg; having a half-life greater than 1 hour), and a process for producing an IαIp composition comprising hydroxylapatite chromatography.

Therefore, because the cited combination of references does not put one of ordinary skill in the art in possession of the claimed invention, one of ordinary skill in the art would not have a reasonable expectation of success in making and using the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 under 35 U.S.C. §103.

CONCLUSION

Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the application with claims 1, 2, 10, 12-15, 21, 25, 27, 28, 31, 40-42, 45-48, 56, 57, 77-86, and 101 presented herein. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Applicants believe no fees are required for consideration and entry of this paper. Nevertheless, Applicants hereby authorize the Director to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 61959(51580).

In view of the above amendments and remarks, Applicants believe the application is in condition for allowance.

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Respectfully submitted,

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